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Nucleophilic substitution at an sp^2 carbon of vinyl halides with an intramolecular thiolate moiety: synthesis of 2-alkylidenethietanes

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This Letter is dedicated to Professor E. J. Corey on the occasion of his 80th birthday

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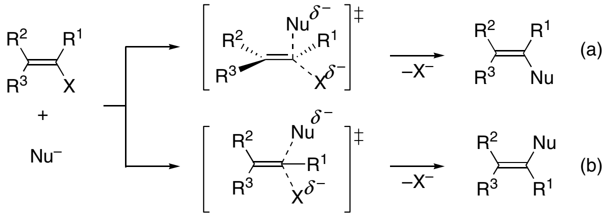
Density functional theory (DFT)

ABSTRACT

Various 2-alkylidenethietanes were synthesized by intramolecular nucleophilic substitution reactions at an sp^2 carbon of vinyl halides with thiolate moieties. The reaction pathway of the substitution reactions was confirmed as a very rare $S_NV\pi$ mechanism by theoretical and experimental studies.

Concerted nucleophilic substitution at an sp^3 carbon, typically an S_N2 reaction, is one of the most fundamental reactions in organic chemistry, giving a substitution product with inversion of the configuration.[1] On the other hand, two mechanisms are proposed for concerted S_N2 reaction at a vinylic sp^2 carbon,[2] namely, the $S_NV\pi$ and $S_NV\sigma$ pathways. In the $S_NV\pi$ mechanism, a nucleophile interacts with the π^* orbital of the vinylic carbon and gives a substitution product with retention of the configuration (Scheme 1a). In the $S_NV\sigma$ mechanism, a nucleophile attacks at the σ^* orbital of the C–X bond and substitution occurs with inversion of the configuration (Scheme 1b). However, both $S_NV\sigma$ and $S_NV\pi$ mechanisms were so far considered as unfavorable processes at unactivated vinylic carbons.[3]



(Nu⁻ = nucleophile; X = leaving group)

Scheme 1.

Recent theoretical studies have indicated the possibilities of the $S_NV\sigma$ and $S_NV\pi$ mechanisms on unactivated vinylic carbons.[4] For example, theoretical calculations performed by Glukhovtsev show that the activation energy of in-plane nucleophilic attack ($S_NV\sigma$) of a chlorine ion to chloroethene ($32.6\ \text{kcal mol}^{-1}$) is about $10\ \text{kcal mol}^{-1}$ lower compared to the out-of-plane attack ($S_NV\pi$) ($42.7\ \text{kcal mol}^{-1}$).[4a] Lee reported that in the gas-phase vinylic substitution of chloroethene by OH^- and SH^-, the $S_NV\pi$ mechanism is favored, whereas the $S_NV\sigma$ pathway is preferred by Cl^- and Br^-.[4c] However, estimated activation energies of both reaction pathways in those theoretical studies were so high that the substitution reactions hardly proceed under the mild reaction conditions. There are a few reports on substitution reactions at an sp^2 carbon atom, which suggested that the reaction proceeded in an $S_NV\sigma$ manner.[5] The substitution reaction of alkenyliodonium salts was found to give the products with inversion of the stereochemistry via an intermolecular $S_NV\sigma$ mechanism.[6] 2-Bromoallylamines were cyclized to aziridines by basic treatment and the stereochemistry of the products suggests that the amino group approaches from behind the bromine atom.[7]

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We recently showed that haloalkenes bearing intramolecular hydroxy, sulfonamide, active methine, and thiol counterparts at suitable positions gave the corresponding 5-membered cyclized products via an intramolecular vinylic substitution reaction.[8] Concerning the cyclizations with O, N, C-nucleophiles, the reactions proceeded only with *E*-isomers to afford the corresponding cyclized products. The *Z*-isomers gave no cyclization products with recovery of the starting haloalkenes (Scheme 2), being consistent with our theoretical studies by DFT calculations.

In contrast, it was found that the cyclization reaction with thiols proceeded with both *E*- and *Z*-isomers in spite of the low product yield (Scheme 3a). The activation energies for the $S_NV\pi$ reactions of thiols were relatively small, which would suggest the $S_NV\pi$ pathway as a possible mechanism. It was also found that a unique 4-membered compound, 2-alkylidenethietane **1a**,[9] was formed in 78% yield by the cyclization of thiol **2a** (Scheme 3b). In this case, only the $S_NV\pi$ type transition structure (activation energy: 20.0 kcal mol^{-1} in DMF) was formed, probably due to steric repulsion between the thiolate and the isopropylidene group.

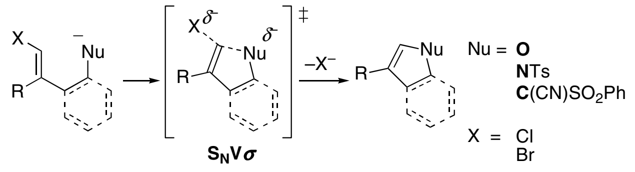
In this Letter, we present a study on the scope of this thietane formation by the cyclization of 3-bromo-3-alkenethiolates and experimental studies to confirm the reaction mechanism.

The synthetic routes to the starting materials are summarized in Schemes 4 and 5. 3-Bromo homoallyl alcohols **5** were synthesized by the reaction of 2,3-dibromopropene (**3**) with aldehydes **4** in the presence of tin powder (Scheme 4a).[10] The reaction of (*Z*)-β-bromoallylsilane **6** with 3-phenylpropionaldehyde (**4g**) gave **5g** with *syn* selectivity (Scheme 4b).[11] These homoallyl alcohols **5** were converted into the corresponding thioacetates **7** by substitution of the intermediate tosylates with potassium thioacetate or by Mitsunobu reaction with thioacetic acid[12] (Scheme 5).

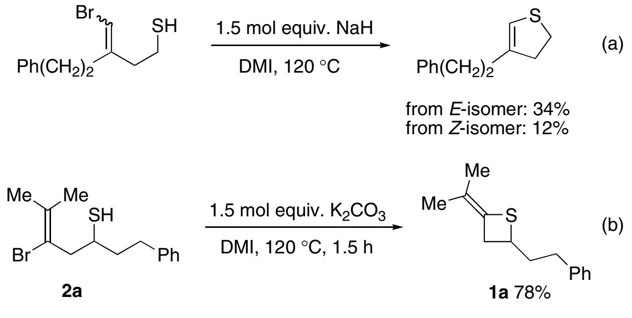
Although the cyclization of tetrasubstituted vinyl bromide **2a** proceeded smoothly (Scheme 3), the cyclization of thiol **2b** with a terminal methylene moiety gave only a trace amount of the desired thietane **1b** in a complex mixture including disulfide **8** (Scheme 6).[13]

We envisioned that generation of the thiolate anion in situ could prevent the formation of disulfide **8**. As expected, when thioacetate **7b** was treated with 1.5 mol equiv of K_2CO_3 and 10 mol equiv of MeOH at 120 °C in degassed DMI, thietane **1b** was obtained in 93% yield (Scheme 7).[14]

Various 2-alkylidenethietanes **1** were synthesized starting from thioacetates **7** by the nucleophilic vinylic substitution reaction

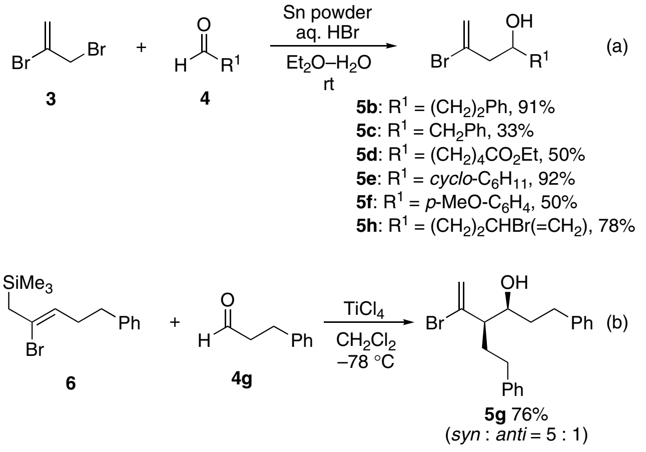


Scheme 2.

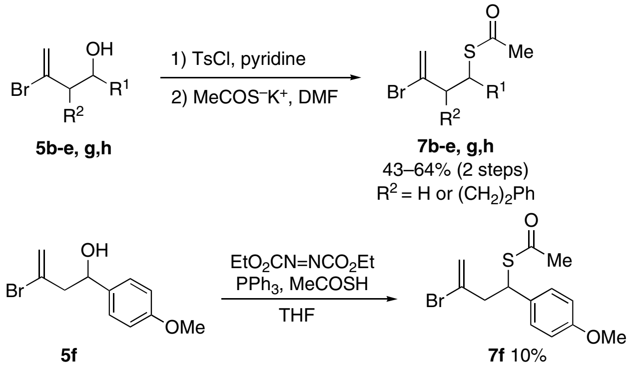


(DMI = *N*,*N*-dimethylimidazolidinone)

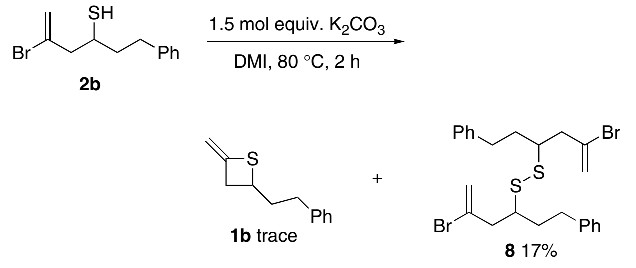
Scheme 3.



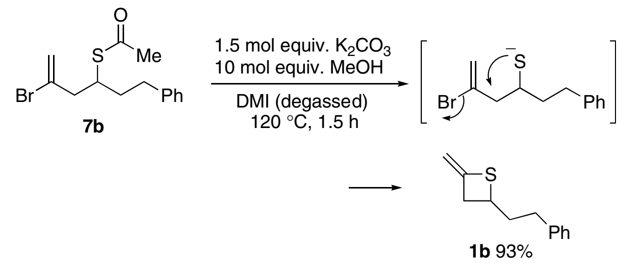
Scheme 4.



Scheme 5.

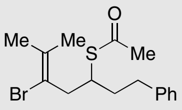
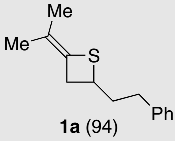
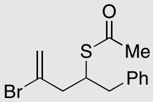
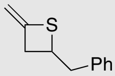
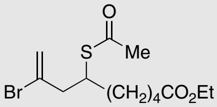
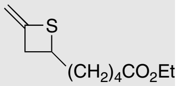
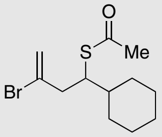
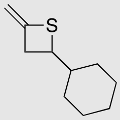
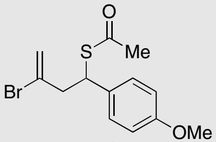
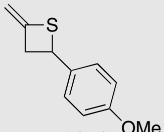
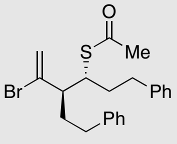
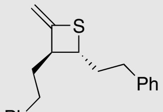


Scheme 6.

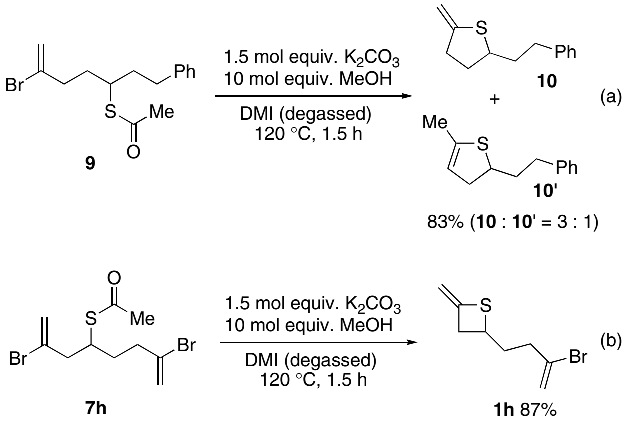


Scheme 7.

Table 1
Synthesis of 2-alkylidenethietanes **1**[a]

Entry	Thioacetate 7	Conditions	Thietane 1 (yield/%)[b]
1	 **7a**	120 °C, 3 h	 **1a** (94)
2	 **7c**	120 °C, 3 h	 **1c** (92)
3[c]	 **7d**	100 °C, 10 h	 **1d** (67)
4	 **7e**	120 °C, 3 h	 **1e** (<65)[d]
5	 **7f**	120 °C, 2 h	 **1f** (30)
6	 **7g**	120 °C, 1.5 h	 **1g** (92)

[a] Reactions were carried out in degassed DMI with 1.5 mol equiv of K_2CO_3 and 10 mol equiv of MeOH.
[b] Isolated yield.
[c] 10 mol equiv of EtOH was used instead of MeOH.
[d] ^{1}H NMR yield.



Scheme 8.

with intramolecular thiolate moieties, and the results are summarized in Table 1. The yield of thietane **1a** was improved to 94% by the use of thioacetate **7a** (Table 1, entry 1). 2-Methylenethietanes **1** possessing primary and secondary alkyl groups at the C(4)-position could be synthesized in good yield (entries 2–4). Benzylic thioacetate **7f** was cyclized to thietane **1f** in moderate yield due to the concurrent elimination of thioacetic acid, forming a conjugated diene as a side product (entry 5). 3,4-Dialkylsubstituted 2-methylenethietane **1g**[15] was formed smoothly in 92% yield (entry 6).

Formation of a 5-membered ring proceeded from thioacetate **9**[16] to give a mixture of 2-methylenetetrahydrothiophene **10** and 2,3-dihydrothiophene **10**′ in 83% yield (Scheme 8a). This result prompted us to try a competition reaction among 4- versus 5-membered ring formation. It was noted that the reaction of thioacetate **7h** gave only 4-membered ring product **1h** without any 5-membered ring compound (Scheme 8b).

Next, we explored theoretical calculations[17] using the GAUSSIAN program.[18] All calculations were performed at the B3LYP[19]/6-31+G(d) level and the solvent effect was included by using the Onsager continuum model[20] for DMF ($\varepsilon = 37.06$) as a solvent.[21] Interestingly, the cyclization of thiolate anion **11** from **7a** gave the $S_NV\sigma$ and $S_NV\pi$ transition states (Fig. 1), both of which have low enough activation energies (22.4 kcal mol^{-1} for $S_NV\sigma$, 18.2 kcal mol^{-1} for $S_NV\pi$) to undergo substitution reactions under the presented reaction conditions.

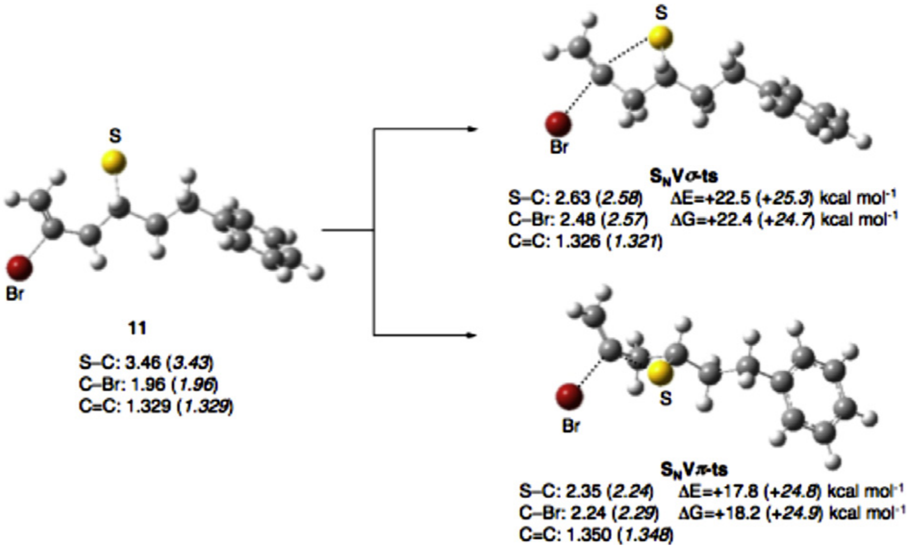
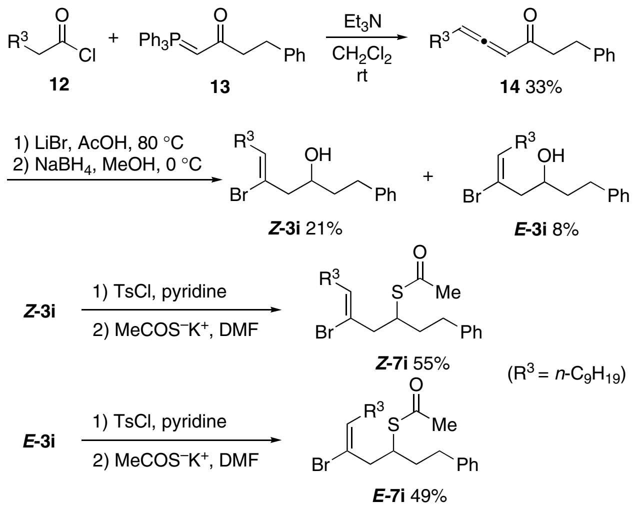
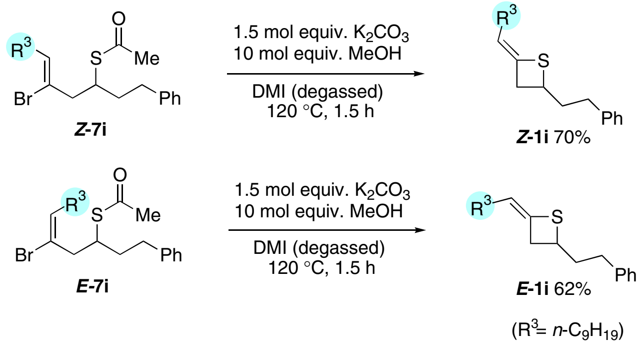


Figure 1. Transition structures for the nucleophilic cyclization of thiolate anion **11** [B3LYP/6-31+G(d), SCRF (dipole, solv = DMF)]. Selected bond lengths are shown in Å. The italicized numbers are the values in the gas phase.



Scheme 9.



Scheme 10.

We envisaged that the reaction mechanism could be confirmed by examination of the stereochemical outcomes of two reaction pathways, that is, the inversion of the configuration for $S_NV\sigma$ and the retention for $S_NV\pi$. Thus, the *Z*- and *E*-isomers of thioacetates **7i** were used for the substitution reactions to clarify the reaction mechanism. The syntheses of *Z*-**7i** and *E*-**7i** are shown in Scheme 9. Allene **14**, synthesized from undecanoyl chloride (**12**) and phosphorous ylide **13**,[22] was treated with LiBr in acetic acid,[23] and then $NaBH_4$ to afford both the *Z*- and *E*- isomers of homoallyl alcohol **3i**, which were transformed to thioacetates **7i** following Scheme 5.[24]

The cyclization of *Z*-**7i** and *E*-**7i** yielded thietanes *Z*-**1i** and *E*-**1i**, respectively, with complete stereospecificity (Scheme 10).[25] These results suggest that the present cyclization proceeds with retention of the configuration, namely by the $S_NV\pi$ mechanism.

Acknowledgment

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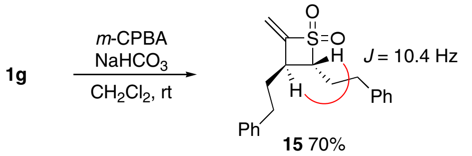
13. Treatment of thiol **2b** with K_2CO_3 even at room temperature gave a complex mixture including disulfide **8**.
14. Experimental procedure for nucleophilic substitution of thioacetate **7b** to 2-alkylidenethietane **1b**: To a solution of thioacetate **7b** (103 mg, 0.329 mmol) and MeOH (103 mg, 3.21 mmol) in DMI (16.5 mL) was added K_2CO_3 (68 mg, 0.492 mmol), and the mixture was stirred at 120 °C for 1.5 h. The reaction was quenched by adding pH 9 ammonium buffer solution at 0 °C, and extracted three times with diethyl ether. The combined extracts were washed with H_2O and brine, and dried over $MgSO_4$. The solvent was removed in vacuo, and the resulting crude products were purified by flash column chromatography (silica gel; hexane/acetone/triethylamine = 95:5:2) to give 2-alkylidenethietane **1b** (56 mg, 0.293 mmol) in 93% yield. Pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (2H, dd, *J* = 7.3, 7.5), 7.20 (1H, t, *J* = 7.3), 7.14–7.16 (2H, m), 4.94 (1H, ddd, *J* = 2.0, 2.1, 2.2), 4.71 (1H, ddd, *J* = 2.2, 2.4, 2.5), 3.60–3.65 (1H, m), 3.58 (1H, dddd, *J* = 2.1, 2.2, 7.1, 7.6), 3.14 (1H, dddd, *J* = 2.0, 2.4, 7.1, 14.8), 2.62–2.68 (1H, m), 2.53–2.59 (1H, m), 2.07–2.20 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.0, 141.0, 128.4 (overlapped), 126.0, 103.5, 43.5, 40.3, 37.9, 33.5; IR (ZnSe) 3026, 2917, 2852, 1631, 1496, 1454, 1120, 1076, 1030, 831, 748, 698, 650 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{12}H_{15}S$ (M+H$^+$): 191.0894, found: 191.0867.
15. The stereochemistry of **1g** was confirmed by the vicinal coupling constant (*J* = 10.4 Hz) of the corresponding sulfone **15**, which was prepared by oxidation of **1g** with *m*-chloroperbenzoic acid (*m*-CPBA) as shown below.



16. Thioacetate **9** was prepared by the same procedure as Scheme 5 from the corresponding alcohol, which can be synthesized by the reaction of 4-bromo-4-pentenal with phenethylmagnesium bromide.
17. The presented calculation is the same as that in our previous articles, see Ref. 8.
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21. DMI has almost the same dielectric constant (37.60) as DMF. Since DMF and DMI are able to dissolve many salts and tend to surround metal cations rather than nucleophilic anions, the use of free anions as model systems may be suitable.

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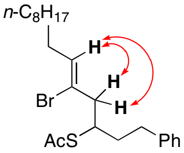
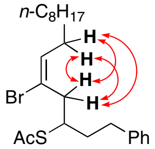
23. Ma, S.; Xie, H.; Wang, G.; Zhang, J.; Shi, Z. *Synthesis* **2001**, *5*, 713.
24. The stereochemistries of the alkenes **7i** were determined by NOE measurements as shown below.

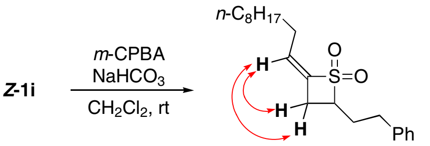


***Z*-7i**

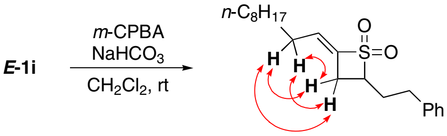


***E*-7i**

25. The stereochemistries of the alkenes **1i** were determined by NOE measurements of the corresponding sulfones **16**, which were prepared by oxidation of **1i** with *m*-chloroperbenzoic acid (*m*-CPBA).



***Z*-16** 81%



***E*-16** 85%